Q fever in Zimbabwe

A review of the disease and the results of a serosurvey of humans, cattle, goats and dogs

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Abstract **Sera from 494 humans, 180 cattle, 180 goats and 27 dogs, collected from different regions of Zimbabwe, were examined by indirect fluorescence for antibodies reactive with phase II *Coxiella burnetii* antigen. Overall, 37% of humans were reactive at a titre of 1/40 or greater, and there was no evidence of age- or sex-related differences in seroprevalence. A review of clinical and epidemiological features of Q fever is presented in order to alert health workers to this infection, which apparently occurs frequently in Zimbabwe even though clinical cases have not been reported. In animals, serological evidence of Q fever infection was found in 39% of cattle, but only 15% of dogs and 10% of goats. These results suggest that cattle are important reservoirs of *C. burnetii* in Zimbabwe.**

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Since Q fever was first recognised as a disease of man in 1935[1] reports of its occurrence have been made from most parts of the world.[2] The causative agent, *Coxiella burnetii*, is an obligate intracellular rickettsial organism which completes its developmental cycle in the phagolysosome of the eukaryotic cell.[3]

Although *C. burnetii* has been isolated from a wide variety of vertebrate and invertebrate hosts[4] it is generally accepted that only ticks and domestic animals are important reservoirs of infection for man. Many tick species have been found to be infected with *C. burnetii* and large numbers of viable organisms are present in their faeces.[5] After natural infection of cattle, sheep or goats the placenta and milk may become grossly infected with organisms[6] but only rarely are abortions, agalactia or other symptoms reported.[6-9]

It is generally accepted that most human clinical cases of Q fever result from infection of the respiratory tract via inhalation of organisms originating from tick faeces or the placenta, birth fluid, faeces, urine, wool, hides or milk of infected animals. In addition, however, intra-uterine or neonatal infections may be possible, since *C. burnetii* has been isolated from human placentas[11] and breast-milk.[10-12] It should be noted, however, that asymptomatic infections may be acquired in other ways, in particular via the digestive tract as discussed below.

In humans, most cases of Q fever occur sporadically, but a number of disease outbreaks have been reported. Often these have involved people in high-risk occupations where there is direct contact with animals or their products, such as workers in meat[1] or milk processing plants,[13] slaughterhouses,[14] veterinary schools[15] and research centres.[15-17] Outbreaks have also been reported from people with only indirect exposure to animals, including inhabitants of a village through which infected sheep were herded,[18] golf players on a course previously used as sheep pastures,[19] military personnel coming into contact with infected hay and straw[20] and poker players exposed to a parturient cat.[21]

Man is the only host of *C. burnetii* known regularly to develop clinical symptoms of infection.[6] The disease is highly infectious with a minimum infective dose of less than two viable organisms,[22] and has been reported in humans of all ages, including infants as young as 5 months.[23] The incubation period of acute Q fever is 14 - 26 days (average 20 days) depending on the route of exposure, inoculum dose and age of the patient.[24,25]

After infection a variety of clinical symptoms may be seen. There is an inverse relationship between severity of disease and age,[26] and many cases are asymptomatic or mild and self-limiting with the patient not seeking medical attention. Fever (> 37,3°C), which is present in all symptomatic cases, may last for 5 - 57 (median 10) days.[26] Other clinical symptoms include headache, chills, sweating, cough, nausea and bradycardia relative to body temperature.[27] During the febrile stage organisms can be isolated from the blood and urine of most patients.[26]

Reports indicate that *C. burnetii* is an important primary cause of pneumonia[28,29] and hepatic disease.[28,30,31] The prevalence of pulmonary and hepatic involvement in the acute stages of Q fever seems to vary with geographical location. For example, respiratory disease was noted in 75% of patients from the Basque region of Spain,[28] compared with only 28% of patients from California[32] and 4% of patients from Australia.[33] Conversely, hepatomegaly was reported in 65% of patients from Australia[30] but only 11% of patients from California.[32] The reasons for this geographical variation may include strain variation in the organism as well as the source, route and dose of infection.[34] After a report that 13% of patients with a presumptive diagnosis of infectious hepatitis had serological evidence of acute Q fever,[35] it has been suggested that Q fever should be considered as a differential diagnosis in all patients with abnormal liver function tests when serological evidence of hepatitis A and B are absent.[34] Characteristic fibrin ring granulomas have been described in histological specimens from patients with acute Q fever.[36]

After the acute stage of Q fever, which lasts for about 3 weeks (range 7 - 60 days), the majority of patients recover from the infection,[37] but *C. burnetii* organisms may persist in the tissues for relatively long periods of time.[3] In rare instances, patients may develop chronic Q fever as long as 20 years after the acute disease.[38] Endocarditis, usually in patients with previously existing valvular disease, is the most common manifestation of chronic Q fever[34] and should be suspected in all cases of endocarditis where blood cultures are repeatedly negative. Common clinical manifestations of endocarditis are fever, splenomegaly[39] and hepatomegaly with lymphocyte infiltration and spotty necrosis in the liver on histopathological examination.[40] Q fever endocarditis

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has a poor prognosis despite therapy and is usually fatal.[34] Occasionally chronic Q fever has been associated with osteomyelitis,[41] chronic hepatitis,[42] haematological abnormalities[43,44] or encephalitis.[45]

The diagnosis of Q fever requires a high index of suspicion and in endemic areas serological testing of patients with clinical symptoms consistent with Q fever is recommended. The suspicion of acute Q fever is not dependent on a history of exposure to animals, since organisms may persist in the environment for many years and people may therefore be exposed to the organism in areas where animals are no longer present. Similarly, clinical symptoms are not pathognomonic and may readily be confused with influenza or other rickettsial diseases, since maculopapular skin lesions may be present in 20% of Q fever patients.[19]

A unique feature of *C. burnetii* is its antigenic phase variation.[46] Phase I *C. burnetii* are virulent organisms which can be isolated from acutely infected animals. Phase II organisms can be obtained after serial passage in immunologically incompetent hosts such as eggs or tissue culture. In cases of acute Q fever, IgM antibodies to *C. burnetii* appear within 1 week of the onset of symptoms and then persist for 10 - 12 weeks.[47] Antibody titres to phase II antigens are generally much higher than to phase I antigens.[47] IgG titres to phase II *C. burnetii* develop slightly later and peak at about 8 weeks after the onset of symptoms. Thereafter the titres decline but may persist for years, or even for life.[48] Titres to phase I *C. burnetii* increase very slowly after acute Q fever and remain at much lower levels than the phase II IgG titres by 1 year after the onset of symptoms.[47] In chronic Q fever patients, IgG antibody titres to both phase I and phase II *C. burnetii* are very high, generally being greater than 1/800.[49] The serological diagnosis of acute Q fever is based on elevated IgG ($\geq$ 1/200) and IgM ($\geq$ 1/25) titres to phase II *C. burnetii* antigens, while the diagnosis of chronic Q fever is based on very high IgG (> 1/800) titres to both phase I and phase II antigens.

Since acute infections are mainly self-limiting it is difficult to establish the efficacy of antibiotic therapy. *In vitro* studies have shown that rifampicin, doxycycline and oxytetracycline[50] and quinolones[51] are rickettsiostatic. Early treatment of acute Q fever with doxycycline or tetracycline reduces the duration of fever,[31,52] although it is not known whether this correlates with elimination of organisms. The benefit of antimicrobial therapy in chronic Q fever endocarditis is even more questionable. Long-term therapy with combinations of doxycycline plus rifampicin[53] or trimethoprim-sulphamethoxazole alone[54] or in combination with tetracycline[55] and tetracycline and lincomycin[42] has been described and reported effective. Even with optimal recommended treatment, rickettsiae can still be demonstrated in patients months or even years later.[34]

Clinical cases of Q fever have been reported from several countries in southern Africa, and serological surveys have indicated that the disease occurs in man and animals in Namibia, South Africa and Malawi. As far as we can ascertain, neither clinical cases nor serological studies have been reported from Zimbabwe. As part of a wider programme investigating the significance of rickettsial and other tick-borne infections in Zimbabwe, we report on a serosurvey for antibodies to *C. burnetii* in man and animals.

Material and methods

Human blood samples were obtained from various sources including healthy blood donors, agricultural workers, schoolteachers and schoolchildren from areas of Zimbabwe representing large urban centres (Harare and Bulawayo), small urban centres (Gweru, Masvingo and Mutare) and rural communities in the north (Karoi, Kariba and Gokwe) and south (Chimanimani, Cashel and Chisumbanje) of the country (Fig. 1). Cattle blood samples, collected at dip tanks around Zimbabwe, were provided by Dr Madsen, Veterinary Research Laboratories, Harare. Dog blood samples were collected from healthy dogs presenting to the Veterinary Teaching Hospital at the University of Zimbabwe. Goat blood, collected from healthy goats in the communal areas of Zimbabwe, was provided by Professor F. W. G. Hill, Faculty of Veterinary Science, University of Zimbabwe.

In each case, sera were separated and stored at -20°C

FIG. 1
Study areas.

before testing by indirect immunofluorescence using phase II *C. burnetii* antigen (Nine Mile strain) obtained from the Centre National de Reference des Rickettsioses, Hôpital de la Timone, Marseilles, France. Fluorescein-labelled antibodies to human or animal IgG (Kirkegaard & Perry Laboratories, Maryland, USA) were used at appropriate dilutions determined from checkerboard titrations. Tests were carried out according to standard procedures and fluorescence was detected using a Leitz UV microscope at × 1 000 magnification.

Results

Antibodies reactive with phase II *C. burnetii* (Table I) were detectable at a titre of $\geq$ 1/40 in human sera throughout Zimbabwe with an overall prevalence of 38% (187/494). High seroprevalences were noted in the urban centres of Harare, Bulawayo and Masvingo, but low seroprevalences were found in rural areas of the south and north (Fig. 1). With sera collected from people whose age was recorded (307) there was no apparent relationship between age and infection, 35 of 124 subjects 20 years or younger (28%) being seropositive compared with 34 of 123 subjects aged 21 - 30 years (28%) and 27 of 90 subjects over 30 years (30%). There was also no indication that acute infections (as determined by antibody titres of $\geq$ 1/160) were more common in any of the age groups. The seroprevalence in males (33%) was not significantly different from that in females (41%) (χ^2 = 1,7; NS). The antibody titres to phase II *C. burnetii* were generally low, with only 29 of 494 sera (6%) being reactive at $\geq$ 1/160.

Overall 4 of 27 dogs (15%) and 18 of 180 goats

TABLE I.
Seroprevalence of Q fever infections in man

		Reciprocal titre											
		> 40		< 40		40		80		160		320	
Location*	No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Harare	189	89	47	100	53	55	29	18	10	11	6	5	3
Bulawayo	42	19	45	23	55	12	29	7	17				
Gweru	40	8	20	32	80	6	15	2	5				
Gokwe	38	11	29	27	71	9	24	2	5				
Kariba	27	10	37	17	63	7	26	2	7	1	4		
Karoi	20	8	40	12	60	6	30	2	10				
Masvingo	67	30	45	37	55	10	15	10	15	3	4	7	10
Mutare	27	4	15	23	85	1	4	2	8	1	4		
Chimanimani	15	3	20	12	80	3	20						
Cashel	10	1	10	9	90	1	10						
Chisumbanje	19	4	21	15	79	3	16	1	5				

* See Fig. 1.

TABLE II.
Seroprevalence of Q fever infections in animals

			Reciprocal titre							
			> 40		< 40		80		≥ 160	
Animal	Location*	No.	No.	%	No.	%	No.	%	No.	%
Dogs	Harare	27	4	15	23	85	4	15	0	
Goats	Siabuwa	20	0		20	100	0		0	
	Bulawayo	20	0		20	100	0		0	
	Chibi	20	0		20	100	0		0	
	Mangwende	20	0		20	100	0		0	
	Goromonzi	20	2	10	18	90	1	5	1	5
	Nyanga	20	2	10	18	90	1	5	1	5
	Tsholotsho	20	3	15	17	85	3	15	0	
	Mutoko	20	5	25	15	75	4	20	1	5
	Chinhamora	20	6	30	14	70	3	15	3	15
Cattle	Makuti	20	2	10	18	90	0		2	10
	Chimanimani	20	3	15	17	85	2	10	1	5
	Harare	40	13	32	27	68	11	29	2	5
	Tsholotsho	20	8	40	12	60	5	25	3	15
	Mutoko	40	20	50	20	50	12	30	8	20
	Bulawayo	20	11	55	9	45	7	35	4	20
	Mutare	20	13	65	7	35	10	50	3	15

* See Fig. 1.

(10%) were seropositive, compared with 70 of 180 cattle (39%) (χ^2 = 5,9 and 40,7 respectively; $P < 0,05$). There was no apparent geographical distribution of seropositivity, with low seroprevalences in cattle in the north (Makuti), south-east (Chimanimani) and south-west (Tsholotsho) of the country (Table II). In goats, infection seemed to occur sporadically with 11 of 40 goats in Mutoko and Chinamhora positive, compared with only 2 of 40 goats in the adjacent areas of Mangwende and Goromonzi (χ^2 = 8,3; $P < 0,05$). As with human sera, the titres of antibody were low with none of 27 dogs, 6 of 180 goats and 23 of 180 cattle reactive at serum dilutions ≥ 1/160.

Discussion

Clinical cases of Q fever have been reported in South Africa[27,56,57] and Kenya[58] but not in Zimbabwe. According to Gear,[57] Q fever is so prevalent in South Africa that most adult South Africans can be regarded as immune and clinical disease is seen mainly in children and recent immigrants. Similar conclusions were reached by Taylor *et al.*[59] after their studies in Egypt and Sudan. Human seroprevalence studies elsewhere in Africa have indicated infection to be rare in Namibia (3%)[60] and Tanzania (4%)[61] but high in Nigeria (22% - 44%)[62,63] and southern Sudan (39%).[64]

Although there have been no reports of Q fever in domestic animals in Zimbabwe, in South Africa infections have been demonstrated in cattle and sheep[65] and serological studies have demonstrated antibodies reactive with *C. burnetii* in 8% of cattle.[66] The seroprevalence in domestic animals in other African countries ranges from 40% for cattle and 53% for goats in southern Sudan[64] to 13% for cattle and 14% for goats in Tanzania[61] and 2% for cattle in Malawi.[67]

The coincidence of the distribution of *Boophilus* ticks and a high seroprevalence in cattle led to the suggestion that these ticks may play a role in the transmission and maintenance of *C. burnetii* infection in cattle in the Transvaal.[65] Although many tick species have been found to be infected with *C. burnetii* (Babudieri), there is little evidence to suggest that tick bites are responsible for human infections.[5] The faeces of ticks infected with *C. burnetii* are heavily contaminated with organisms, which remain viable in the faeces for long periods of time and therefore may be a potential source of infection for man and animals.[19] Such infected faeces may become powdered and windborne thereby infecting the upper respiratory tract of man and animals. Studies on the role of ticks in the epidemiology of *C. burnetii* and other rickettsias are currently being undertaken in our laboratory.

The obvious question that arises from our findings is why there are no clinical reports of Q fever in Zimbabwe when the serological evidence indicates that infection with *C. burnetii* occurs not infrequently. There are a number of possible explanations. Firstly Q fever infections are often asymptomatic, especially in children. In an outbreak of Q fever in Switzerland it was shown that of the 415 people diagnosed as having been exposed to *C. burnetii*, 54% were asymptomatic and of the 191 symptomatic cases only 8 required hospitalisation.[68] Secondly, since acute Q fever has nonspecific symptoms, is often mild and self-limiting and closely resembles influenza in presentation, many cases are probably misdiagnosed because of a low index of suspicion. Even where Q fever may be suspected the complement fixation test, currently in use, has been shown to be less reliable than indirect fluorescent antibody (IFA) testing in diagnosing acute infections because of the anticomplementary activity in the sera of Q fever patients.[49] Also, the complement fixation test has lower sensitivity than the IFA test.[69]

Other explanations include the route of infection and strain variation. In man, *C. burnetii* infection usually occurs as a result of ingestion or inhalation of infected material. A large percentage of cows infected with *C. burnetii* shed viable organisms in their milk for months and sometimes years after infection, but only a few cases of clinical Q fever have been ascribed to the ingestion of infected raw milk. It is possible that the antibody-coated organisms that appear in milk result in subclinical rather than clinical infections and that infected milk 'may be vaccinating more people than it is infecting'.[19]

Finally, studies elsewhere have documented wide variation in clinical presentation in different geographical locations, suggesting that there may be strain differences in infecting organisms. In our serosurvey we found no evidence of chronic infection, as determined by high titres of IgG to phase II antigen, and the local strain may then be of low virulence. It would be prudent, however, to include Q fever serological tests in the investigation of patients with abacteraemic endocarditis. We are currently investigating the sera of patients with endocarditis and hepatitis in order to assess the importance of Q fever as an aetiological agent in these conditions.

In summary, our results show that exposure to *C. burnetii* is common in man and in cattle in Zimbabwe, but relatively uncommon in goats and dogs. Because of the close association between people and cattle in the country it appears likely that cattle are the main reservoirs of infection.

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